Remarks

Claims 1, 14-18, 27, 41-44, 54, and 55 were pending in the application. No claim amendments are made herein. Therefore, **claims 1, 14-18, 27, 41-44, 54, and 55** remain pending in this application. Re-consideration of the pending claims is requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 14-18, 27, 41-44, 54, and 55 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mor (U.S. Pat. Publ. No. 2003/0157573), further in view of Klinghoffer *et al.* (U.S. Pat. Publ. No. 2004/0077574), further in view of O'Donnell *et al.* (*Am. J. Pathol.* 154:1171-1180, 1999), and further in view of Varner and Cheresh (*Curr. Opin. Cell Biol.* 8:724-730, 1996). Applicants traverse and request reconsideration.

The analysis for determining obviousness under 35 U.S.C. § 103(a), as articulated in *Graham v. John Deere Co.* 383 U.S. 1 (1966), requires 1) determining the scope and content of the prior art; 2) ascertaining the differences between the prior art and the claims at issue; and 3) resolving the level of ordinary skill in the pertinent art. *Graham*, 383 U.S. at 7. In particular, ascertaining the differences between the prior art and the claims requires that both the claims and the prior art be read as a whole (M.P.E.P. § 2141.02; *In re Langer*, 465 F.2d 896, 899, 175 USPQ 169, 171 (CCPA 1972); *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1551, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). "All of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art…[W]hen 'all of the disclosures in a reference' are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference." *In re Langer*, 465 F. 2d at 899, 175 USPQ at 171.

The Office asserts that it would have been *prima facie* obvious to combine the teachings of Mor and Klinghoffer *et al.* to use RNAi molecules in the screening methods of Mor to identify effective anti-angiogenic drugs (Office action, page 4, first full paragraph). The Office states that one of skill in the art would have been motivated to combine these references in order to identify the most effective angiogenesis inhibitor and would have had a reasonable expectation of success (Office action, page 4, first full paragraph).

The combination of Mor and Klinghoffer *et al.* does not include all of the limitations of the pending claims. The Office acknowledges that Mor does not disclose a method that includes assaying $\alpha v\beta 3$ expression, tube formation, or haptotaxis (Office action, page 3, third full paragraph). Klinghoffer *et al.* disclose siRNAs and their use as therapeutics for a range of diseases, but likewise does not disclose methods that include assaying $\alpha v\beta 3$ expression, tube formation, or haptotaxis. Thus, the combined references do not disclose all the limitations of Applicants' claims, and the Office has not set forth a reason that one of ordinary skill in the art would have modified these references to arrive at Applicants' claims. Therefore, the Office has not established a *prima facie* case of obviousness.

Furthermore, Mor is focused on identifying inhibitors of Axl for use in treating fibrosis (particularly renal fibrosis) and glomerulosclerosis (Mor, paragraphs [0033] and [0036]). These conditions are characterized by proliferation of fibroblasts, overproduction of connective tissue proteins and thickening of the basal membrane of the glomeruli (Mor, paragraph [0007]). In addition, Mor indicates that appropriate cell-based assays for measuring Axl activity include cell survival, cellular differentiation, and cell proliferation (Mor, paragraph [0059]). Mor states that compounds identified in its screen may be useful for treating nephropathy, kidney fibrosis and other fibrotic diseases, and restenosis, which is a proliferation of smooth muscle cells (Mor, paragraph [0090]). Finally, Mor states that the compounds "may also be used as anti-angiogenic drugs for the treatment of cancer and other conditions where preventing or reducing *proliferation* of endothelial cells is desired" (Mor, paragraph [0090], emphasis added). Taken as a whole (as required by the M.P.E.P and case law, as cited above), Mor discloses an assay for identifying inhibitors of Axl utilizing *cell proliferation* as the indicator of Axl activity, rather than an assay for identifying inhibitors of *angiogenesis*, as recited in Applicants' claims. Klinghoffer *et al.* discloses Axl only as containing a potential PTP1B domain (paragraph [0016]), and does not suggest any role of Axl in angiogenesis.

One of skill in the art might have been motivated utilize the methods disclosed in Mor and Klinghoffer *et al.* to identify an siRNA inhibitor of Axl which inhibits cell proliferation with a reasonable expectation of success. However, the disclosure by Mor that an inhibitor of Axl

could be identified by assaying cell proliferation, even proliferation of endothelial cells, does not make it predictable that a compound identified by such a method would inhibit an angiogenesis phenotype such as αvβ3 expression, tube formation, or haptotaxis in endothelial cells expressing Axl (despite the use of the term "anti-angiogenic" by Mor in paragraph [0090]). Thus, one of skill in the art would not have been motivated to modify the methods disclosed in Mor to assay αvβ3 expression, tube formation, or haptotaxis in combination with Klinghoffer *et al.* to identify an inhibitor of angiogenesis, particularly when Mor is considered as a whole. Therefore, Applicants' claims are not obvious over the combination of Mor and Klinghoffer *et al.* and withdrawal of this rejection is requested.

The Office also asserts that it would have been *prima facie* obvious to combine the teachings of Mor, O'Donnell *et al.*, and Varner and Cheresh to measure αvβ3 expression or tube formation in endothelial cells because "Mor teaches assaying cellular differentiation…, O'Donnell *et al.* teaches that Axl may be involved in tube formation during angiogenesis, and Varner and Cheresh teach that αvβ3 expression is [a] critical event of blood vessel formation…" (Office action, page 4, second full paragraph). The Office also asserts that Varner and Cheresh disclose that αvβ3 "is important [in] endothelial cell survival (like Axl), and inhibition of αvβ3 inhibits angiogenesis" (Office action, page 4, second full paragraph).

Applicants again emphasize that Mor, when read as a whole, teaches methods of identifying inhibitors of Axl by assaying cell proliferation, cell survival, or cellular differentiation in fibroblast or mesangial cells (*e.g.,* paragraph [0059], claims 5-9). Based on Mor, one of skill in the art would not have been motivated to utilize an assay measuring αvβ3 expression, tube formation, or haptotaxis in an endothelial cell expressing Axl to identify an angiogenesis inhibitor. O'Donnell *et al.* describe the expression of Axl in capillary endothelial cells (page 1174, left column) and the role of the Axl ligand Gas6 in increasing endothelial cell survival and/or decreasing endothelial cell apoptosis (page 1175-1176). This is acknowledged by the Office, which states "O'Donnell clearly shows that Axl is expressed in endothelial cells and is involved in their *viability and survival*" (Office action, page 6, second full paragraph, emphasis added). O'Donnell *et al.* speculate that Axl *may* be involved in cell adhesion, and could therefore be "relevant to tube formation in angiogenesis" (page 1176, right column) and

note that Gas6 can elicit chemotaxis of vascular smooth muscle cells (page 1177). However, O'Donnell *et al.* also note that Gas6 is a "promiscuous ligand" for the Axl subfamily (which includes Axl, Sky, and Mer tyrosine kinases) and that "Gas6 has been shown to protect a number of Axl-positive cells from stimuli that induce apoptosis" (page 1178, right column). Other effects of Gas6 (such as chemotaxis) may be due to the "promiscuous" effects of Gas6 and not specific to Axl.

Based on the focus of Mor on Axl inhibitors as potential inhibitors of cell proliferation and that of O'Donnell *et al.* on Axl as a mediator of cell survival, one of skill in the art would not have been prompted to assay markers of angiogenesis such as $\alpha v\beta 3$ expression, tube formation, or haptotaxis in endothelial cells. In particular, the disclosure of O'Donnell *et al.* is highly similar to that of Healy *et al.* (*Am. J. Physiol. Lung Cell Metabol.* 280:L1273-L1281, 2001), which was previously cited by the Office in a rejection under 35 U.S.C. § 103(a) in combination with Varner and Cheresh and Klinghoffer *et al.* (*e.g.,* Office action dated June 23, 2008). That rejection was overturned by the Decision of the Board of Patent Appeals and Interferences (Appeal 2009-011194, March 16, 2010), which stated that "Healy's investigation focused on determining the role Gas6 plays in endothelial cell survival and in Axl-related apoptotic cell death…The Examiner has not adequately explained why an ordinary artisan studying the effects of Gas6 HPAEC on Axl-mediated apoptosis of HPAECs, as taught by Healy, would have been prompted to assay the expression of $\alpha v\beta 3$, an angiogenesis marker, in those cells" (Decision, page 17, last paragraph). Furthermore, one of skill in the art would not have had a reasonable expectation of success that a method including assaying $\alpha v\beta 3$ expression, tube formation, or haptotaxis in endothelial cells expressing Axl would identify an inhibitor of angiogenesis based on the speculative statements included in O'Donnell *et al.* regarding a potential role of Axl in vascular structure and function.

Finally, Varner and Cheresh describe the role of $\alpha v\beta 3$ integrin in the process of angiogenesis (page 726, right column) and disclose that an $\alpha v\beta 3$ antagonist inhibits angiogenesis (page 726-727). However, this reference does not teach or suggest a role for Axl polypeptide in angiogenesis. Therefore, the combination of Varner and Cheresh with Mor and O'Donnell *et al.* does not provide a motivation for one of skill in the art to measure $\alpha v\beta 3$ expression in the assay

of Mor (which as discussed above, is directed to cell proliferation), nor provide a reasonable expectation of success. Therefore, Applicants' claims are not obvious over the combination of Mor, O'Donnell *et al.*, and Varner and Cheresh, and withdrawal of this rejection is requested.

Conclusion

Applicants respectfully submit that the claims are now in condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned to arrange a telephonic interview prior to the preparation of any further written action.

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cc: Docketing